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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/506,978	02/18/00	SPERTINI	F 18519-001

EXAMINER	
HUYNH, P	
ART UNIT	**PAPER NUMBER**
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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/506,978	Applicant(s) SPERTINI, FRANCOIS	
	Examiner " Neon" Phuong Huynh	Art Unit 1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *05 June 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1-46* is/are pending in the application.

4a) Of the above claim(s) *1-27 and 31-35* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *28-30 and 36-46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Preliminary amendment, filed 6/5/01, is acknowledged.
Specification has been amended.
Claims 28-30 have been amended.
Claims 36-46 have been added.
Claims 1-46 are pending.

2. Applicant's election without traverse of Group VI claims 28-30, filed 6/5/01, is acknowledged.

3. It is noted that newly added claim 36 recites the method of claim 28 further comprising administering a one or more additional bee venom polypeptides to the subject; claims 37-40 and 44 recite the method comprising administering a substantially pure polypeptide comprising a fragment of the amino acid sequence of SEQ ID NO: 1 wherein the fragment is between 6-72, 20-72, 30-70 and 40-60 amino acids in length, respectively. Claims 42-43, and 45-46 recite the method further comprised one or more additional bee venom polypeptides wherein the additional bee venom polypeptide are selected from the group consisting of phospholipase A2, hyaluronidase, allergen C, mellitin, adopin, minmine or analogs or derivatives thereof. Therefore, newly added claims 36-46 are being examined along with the elected Group VI, claims 28-30, and 36-46.

4. Claims 1-27 and 31-35 are withdrawn from further consideration by the examiner, 37 C.F.R. 1.142(b) as being drawn to non-elected inventions.

5. Claims 28-30 and 36-46 are being acted upon in this Office Action.

6. The drawing, filed 2/18/00, is approved.

7. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because: Applicant has checked the box for a claim to provisional application under Title 35, United States Code, § 119(e). However, no reference to the provisional application number has been provided to the Office.

8. The disclosure is objected to because of following informalities. (1) Accession No. for hydridoma 5E11 needs to be filled out on page 2 of the specification. (2) The dash line indicating the page number on page 24, line 26 of the specification should be "pp 155-194". (3) The phrase "*Selected_Methods*" on line 28, page 24 should be "*Selected Methods*". (4) SEQ ID NOS are required for Figure under the Brief Description of the Drawings. (5) The "20-90" on page 11, line 22 does not provide support for the claim 39. It is noted that claim 39 recites "20-72". Clarification and/or correction is required.

9. Claims 30, 43 and 46 are objected to because of the limitation "acid phosphatase" is being recited twice in the claims.

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 28-30, 36-46 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of inhibiting T cell response of a mammal sensitive to a protein allergen from bee venom comprising administering a substantially pure polypeptide comprising an amino acid sequence of SEQ ID NO: 1 to a subject in needed thereof to inhibit an immune reaction by the subject against said polypeptide, does not reasonably provide enablement for a method of inhibiting an immune reaction comprising administering *any* polypeptide that is "at least 70% identical" to the amino acid sequence of SEQ ID NO: 1 or *any* fragment of the amino acid sequence of SEQ ID NO: 1 such as between 6-72, 20-72, 30-70 or 40-60 amino acid in length (See page 19 of the specification). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8

USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The scope of the claims encompass a method of inhibiting *any* immune response of a mammal sensitive to a protein allergen from bee venom comprising administering *any* polypeptide comprising an amino acid sequence that is "at least 70% identical" to the amino acid sequence of SEQ ID NO: 1, *any* polypeptide "fragment" of the amino acid sequence of SEQ ID NO: 1, and *any* polypeptide fragment of SEQ ID NO: 1 such as between 6-72, 20-72, 30-70 or 40-60 amino acid in length for a method of inhibiting any immune response by the subject against said polypeptides.

The specification discloses only 4 full-length polypeptides of SEQ ID NOS: 1-4 for a method of inhibiting T cell response in a subject who is sensitive to a protein allergen from bee venom (see page 19).

The specification does not disclose *any* polypeptide comprising an amino acid sequence that is "at least 70% identical" to the amino acid sequence of SEQ ID NO: 1, *any* polypeptide "fragment" of the amino acid sequence of SEQ ID NO: 1 such as between 6-72, 20-72, 30-70 or 40-60 amino acid in length and whether *any* of the polypeptide mentioned above have the same structure and function such as inhibiting any immune response as SEQ ID NO: 1. The specification fails to provide guidance as to how to make and/or use *any* polypeptide "comprising" an amino acid sequence that is "at least 70% identical" to the amino acid sequence of SEQ ID NO: 1", *any* polypeptide comprising a "fragment" of the amino acid sequence of SEQ ID NO: 1, *any* polypeptide fragments of the amino acid sequence of SEQ ID NO: 1 such as between 6-72, 20-72, 30-70 and 40-60 amino acids in length for a method of inhibiting T cell response in a subject against said polypeptides.

It is known that many amino acid substitution, deletion, addition are generally possible in any given polypeptide to generate a polypeptide that is "at least 70% identical" to SEQ ID NO: 1 and *any* polypeptide fragments of SEQ ID NO: 1. However, the amino acid positions within the polypeptide of SEQ ID NO: 1 that can tolerate change such as conservative substitution or no substitution, addition or deletion which are critical to maintain the protein's structure/function will

require guidance (see Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495).

There is no recognition in the art that sequence with identity predicts biological function. It is known in the art that even single amino acid changes or differences in a protein's amino acid sequence can have dramatic effects on the protein's function.

Attwood *et al* teach that "It is presumptuous to make functional assignments merely on the basis of some degree of similarity between sequences (and it is not always clear what we mean by "function"); very few structures are known compared with the number of sequences, and structure prediction methods are unreliable (and knowing structure does not inherently tell us functions)".

Fasler *et al.* teach that peptides derived from house dust mite Der p1 are modified by single amino acid substitutions at positions 173, 175, 176, 180 and 181 with alanine or glycine failed to induce Der p1 specific T cell proliferation and IL-2, IL-4 and IFN-γ production. Fasler *et al.* further teach that substituting a neutral Asn residue at position 173 with either a basic Lysine, a hydrophobic Try, Ile, an acidic Asp or a hydrophilic residue serine also did not induce T cell proliferation and cytokine production. However, substitution amino acid positions other than 173, 175, 176, 180 and 181 induces normal or only slightly reduced proliferative responses and cytokine production by T cells (page 524, in particular).

Burks *et al.* teach a modified allergen from peanut Ara h1 where the immunodominant IgE binding epitope of Ara h1 is modified by amino acid substitution at position 1, 3, 4 and 17 with alanine or glycine reduced IgE binding. In contrast, substituting an alanine for glutamine residue at position 31 leads to an increase IgE binding. Burks *et al.* further teach that "there is no obvious position within each peptide that when mutated, would result in loss of IgE binding and there was no consensus in the type of amino acid that, when changed to alanine, would lead to loss of IgE binding" (See page 338, in particular).

Stanley *et al.* teach a modified peanut allergen Ara h2 by amino acid substitution with alanine at position 67, 68 or 69 significantly reduced IgE binding while substitution of serine residue at position 70 leads to an increased in IgE binding. Stanley et al also teach that in general, "each epitope could be mutated to a non-IgE binding peptide by the substitution of an alanine for a single amino acid residue. However, there was no obvious position within each peptide that, when mutated, would result in loss of IgE binding. Furthermore, there was no

consensus in the type of amino acid that, when changed to alanine, would lead to loss of IgE binding" (See page 251, in particular).

Skolnick *et al* teach that sequence-based methods for function prediction are inadequate and knowing a protein's structure does not tell one its function (See abstract, in particular).

Colman *et al* teach that a single amino acid changes within the interface of antibody-antigen complex can abolish the antibody-antigen interaction or binding entirely (See page 33, in particular).

Therefore, a polypeptide that is "at least 70% identical" to SEQ ID NO: 1 means there is a 30% difference. There is no working examples in the specification as filed to demonstrate any polypeptide with 30% difference to SEQ ID NO: 1 will have similar structure and function to the full-length polypeptide of SEQ ID NO: 1 which inhibits T cell response. Likewise, there are no working examples to demonstrate *any* polypeptide "fragment" of SEQ ID NO: 1 such as between 6-72, 20-72, 30-70 or 40-60 amino acid in length have similar structure and inhibitory T cell response/function as SEQ ID NO: 1. Because the core structural and functional requirements for SEQ ID NO: 1 for inhibiting T cell response are not defined, it is not possible to predict which polypeptide that is "at least 70% identical" to SEQ ID NO: 1 or which "fragment" of the amino acid sequence of SEQ ID NO: 1 such as between 6-72, 20-72, 30-70 and 40-60 amino acid in length will maintain structure and function such as inhibiting T cell response by the subject against said polypeptide.

For these reasons, the specification as filed fails to enable one skill in the art to practice the invention as broadly as claimed without undue amount of experimentation. In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the lack of guidance and the lack of working examples, the breadth of the claims which fail to recite any structural or functional limitations and the unpredictability of the art, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

12. Claims 28-30, 36-46 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The instant claims encompass a method of modulating an immune response comprising administering *any* polypeptide comprising an amino acid sequence "at least 70% identical to the amino acid sequence of SEQ ID NO: 1 or *any* polypeptide "comprising a fragment" of SEQ ID NO: 1, and *any* fragment such as between 6-72, 20-72, 30-70 or 40-60 amino acids in length of SEQ ID NO: 1 to a subject to inhibit any immune response by the subject against said polypeptide.

The specification as filed discloses only four polypeptides of SEQ ID NOS: 1-4 from bee venom for making antibody to said polypeptides and inhibit T cell response in a subject who is sensitive to a protein allergen from bee venom (See page 19).

However, the specification does not reasonably provide a **written description** of *any* additional species of polypeptide comprising an amino acid sequence "at least 70% identical" to the amino acid sequence of SEQ ID NO: 1, *any* fragment of the amino acid sequence of SEQ ID NO: 1, and *any* polypeptide fragment of SEQ ID NO: 1 such as between 6-72, 20-72, 30-70 or 40-60 amino acid in length. Further, there is no disclosure of any particular structure and inhibitory immune function of any of the polypeptide mentioned above. The specification fails to describe additional representative species of these polypeptides by any identifying structural characteristics or functional properties other than the polypeptide comprising an amino acid sequence "at least 70% identical" to the amino acid sequence of SEQ ID NO: 1, *any* "fragment" of the amino acid sequence of SEQ ID NO: 1 and *any* fragments of SEQ ID NO: 1 such as between 6-72, 20-72, 30-70 or 40-60 amino acid in length.

Given this lack of additional representative species as encompassed by the claims, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. *see University of California v. Eli Lilly and Co. 43 USPQ2d 1398.* Applicant is directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, 1 "Written Description" Requirement, Federal Register, Vol. 64, No. 244, pages 71427-71440, Tuesday December 21, 1999.

13. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

14. Claims 37-40 and 44 are rejected under 35 U.S.C. 102(b) as being anticipated by Banks *et al* (Chemistry and Pharmcology of Honey-bee venom In: Piek T, ed. Venoms of the Hyemoptera. London: Academic Press; 1986, pages 329-416).

Banks *et al* teach a method of modulating an immune response (desensitization) comprising administering a small but increasing amounts of allergen (polypeptide from bee venom) to build up the IgG levels in the serum of a subject to inhibit an immune reaction (allergic reaction) against bee sting (See page 342, pages 331 and 403, in particular). Banks *et al* further teach a polypeptide-H1 that is 17 amino acids in length and a polypeptide-H3 that is 31 amino acids in length which both are fragments of polypeptide of SEQ ID NO: 1 as recited in claims 37-40 and 44. The said polypeptide fragments are protease inhibitors, which have protease inhibitory activity toward kallikrein and urokinase activity (See page 398, in particular). Bank *et al* further teach additional polypeptide from bee venom such as phospholipase A2 (the chief allergen in bee venom), hyaluronidase, melittin and protease inhibitor (See Table II, in particular). Thus, the reference teachings anticipate the claimed invention.

15. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

16. Claims 37 and 42-46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Banks *et al* (Chemistry and Pharmcology of Honey-bee venom In: Piek T, ed. Venoms of the Hyemoptera. London: Academic Press; 1986, pages 329-416) in view of U.S. Pat No. 6,074,673, (filed April 1996; PTO 892) or U.S. Pat No. 5,965,709 (Oct 1999; PTO 892).

The Banks *et al* reference has been discussed supra.

The claimed invention as recited in claims 42 and 45 differs from the reference only by the recitation of the method further comprising administering one or more additional bee venom polypeptides to a subject. The claimed invention as recited in claims 43 and 46 differs from the reference only by the recitation of one or more additional bee venom polypeptides are selected from the group consisting of phospholipase A2, hyaluronidase, allergen C, mellitin, adolapin, minimine, acid phosphatase, protease inhibitor, glycosylated IgE-binding proteins, or analogs or derivatives thereof.

The '673 patent teaches a method of modulating an immune response comprising administering an allergy desensitization composition of polypeptides from bee venom such as phospholipase A2, hyaluronidase and mellitin to a subject for inhibiting an immune reaction (inhibit IgE production) to said polypeptides and allergic reaction to bee venom (See column 2, lines 60-65; column 9, line 12; column 10, lines 52-67 bridging column 11 lines 1-6, in particular). The '673 patent further teaches administering a composition containing one or more allergens which are polypeptides from bee venom to a subject (See column 11, lines 57-62, in particular).

The '709 patent teaches IgE antagonists which are analogs and derivatives of IgE binding protein for the treatment of allergic disease (See abstract, column 5, lines 59-60; column 32, lines 51-65, in particular). The '709 patent further teaches the use of IgE antagonist to inhibit the binding of IgE to mast cells and to combine the IgE antagonist with other known therapy (See column 34, lines 4-14, in particular).

Therefore, it is prima facie obvious to one of ordinary skill in the art at the time the invention was made to combine the polypeptide fragments from bee venom as taught by Banks *et al* with the polypeptides from the bee venom such as phospholipase A2, hyaluronidase and mellitin as taught by the '673 patent or the analog or derivatives of the IgE binding protein as taught by the '709 patent for a method of inhibiting an immune reaction (allergic reaction) to bee venom as taught by the '673 patnent (See abstract, in particular) and by the '709 patent for treatment of allergy (See abstract, in particular). It is prima facie obvious to combine two

compositions each of which is taught by the prior art to be useful for the same purpose in order to form a third composition that is to be used for the very same purpose. The idea of combining them flows logically from their having been individually taught in prior art. In re Kerkhoven, 205 USPQ 1069, CCPA 1980. See MPEP 2144.06. One having ordinary skill in the art at the time the invention was made would have been motivated to combine the different polypeptides from bee venom for inhibiting an immune reaction because Banks *et al* teach that phospholipase A2 works synergistically with melittin to cause tissue damage (See page 342, in particular). One having ordinary skill in the art at the time the invention was made would have been motivated to combine one or more additional bee venom polypeptides such as phospholipase A2, hyaluronidase, mellitin as taught by the '673 patent or the IgE analog and derivatives (IgE antagonist) as taught by the '709 patent with the polypeptide fragments as taught by Banks et al with an expectation of success because each of which is taught by the prior art to be useful for inhibiting allergic reaction as taught by Banks et al (See page 342, pages 331 and 403, in particular), inhibiting IgE production as taught by the '673 patent (See column 9, line 12, in particular), inhibiting the binding of IgE to mast cells and to combine the IgE antagonist with other known therapy as taught by the '709 patent (See column 34, lines 4-14, in particular) in order to form a third composition that is to be used for the very same purpose.

17. Claims 28-30, 36 and 41 are free of prior art.

18. No claim is allowed.

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to "Neon" Phuong Huynh whose telephone number is (703) 308-4844. The examiner can normally be reached Monday through Friday from 9:00 am to 6:00 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

20. Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401.

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July 30, 2001

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